REMARKS

Claims 1-11, 17-18, and 20-30 remain pending in this application after entry of the above amendment. Applicants submit that the amendments to claims are fully supported by the application as originally filed. In particular, Applicants submit that the amendments to Claims relating to "functional homologues" are supported by paragraphs 144 to 158 of the specification and the amendment to Claim 10 is supported by paragraph 160 of the specification.

Applicants note that the Examiner has suggested that claims 25-28 are directed to non-elected subject matter and thus are not currently under examination. Applicants respectfully request reconsideration of this position. Specifically, Applicants point out that claims 25-28 depend from claim 24, which in turn depends from claim 1. As the Examiner has accepted that both claims 1 and 24 are within the scope of the elected subject matter, Applicants believe claims 25-28 should also be included in the group currently under examination.

No new matter has been added. In particular, Applicants note that the amendments to the specification, presented above, are included to correct typographical errors and are fully supported by the specification. For example, SEQ ID NO 6 is identified in Fig 16a as "CDR3" rather than "CDR4," and one of skill in the art would immediately recognize that there is no recognized antibody region identified as "CDR4." Furthermore, the changes to Example 6 merely correct typographical errors to bring it into conformity with the information presented on Pages 6-7 and 18-19. Entry of these amendments is requested. Any amendment or cancellation of the claims is made without prejudice to the prosecution of such subject matter in this or other patent applications.

Claim Objections

The Examiner has objected to Claims 12-15, 18 and 19 as containing non-elected subject matter. Applicants submit that, in light of the amendment presented above, the Examiner's objections have been rendered moot and therefore withdrawal of those objections is respectfully requested.

Rejections under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 12-15, 18, 19, and 22 because the specification is allegedly contradictory regarding what is represented by the elected amino acid sequence SEQ ID NO 6. In particular, the Examiner argues that SEQ ID NO 6 is referred to in the sequence listing as "CDR4 anti-PsaA 7-1G9 VK," while pages 18-19 of the of the specification refer to SEQ ID NO 6 as CDR3 of the 9A7 antibody sequence included in Figure 16A. As outlined in the amendment to the specification presented above, the typographical errors giving rise to the Examiner's confusion have been corrected and therefore withdrawal of this rejection is respectfully requested.

Claims 1-15, 17-24, and 29-30 stand rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner argues that "the claims as written relate to any possible product with desirable binding characteristic or property whereas the disclosure provides support for a limited number of such products relating to a polypeptide that can bind to an epitope on a Streptococcus pneumoniae protein." (See page 3 of the instant Office Action). Without acquiescing in the propriety of the Examiner's position, and solely to expedite the prosecution of the instant application, Applicants have amended the pending claims such that they refer to an "isolated binding polypeptide." Accordingly, Applicants respectfully request withdrawal of this rejection.

The Examiner has rejected claim 10 under 35 U.S.C. §112, second paragraph as allegedly being indefinite. In particular, the Examiner contends that Claim 10 is indefinite due to its reference to "N-terminal part" of the PsaA protein. Applicants submit that the amendment to Claim 10, which specifically identifies the N-terminal 150 amino acid portion of the PsaA polypeptide, renders the instant rejection moot. Accordingly, Applicants respectfully request withdrawal of this rejection.

The Examiner has rejected claims 12-15 under 35 U.S.C. §112, second paragraph as allegedly being vague and indefinite. In particular, the Examiner contends that the metes and bounds of the term "homologue" cannot be understood. Applicants respectfully point out that the claims have been amended to refer only to "functional" homologues, which are described in paragraphs 144 to 158 of the instant specification as a sequence that "may vary in one or more

amino acids as compared to the sequences defined, but is capable of performing the same function, i.e. a homologue may be envisaged as a functional equivalent of a predetermined sequence."

Rejections under 35 U.S.C. §112, first paragraph, enablement

The Examiner has rejected claims 12-15, 18, and 19 under 35 U.S.C. §112, first paragraph, as allegedly failing to enable a person skilled in the art to make and/or use the invention commensurate in scope with the claims. In particular, the Examiner argues that because the claims are directed to sequences that may have one or more amino acid substitutions ("functional homologues"), that the claims encompass in their breadth a variety of sequences which cannot be sufficiently predicted due to the alleged lack of guidance contained in the specification regarding acceptable amino acid substitutions, additions, or deletions.

Applicants respectfully disagree with the Examiner's conclusion and submit that the claims are fully supported by an enabling disclosure. As stated in the M.P.E.P., "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."[1] The instant specification provides ample disclosures of antibodies with amino acid sequences that have the ability to bind to PsaA protein (See Figures 16-18). A person of ordinary skill in the art would not have to "predict" which substitutions would result in an antibody capable of specifically binding PsaA protein. Instead, the skilled artisan would be able to employ routine methods that are described in the specification or otherwise known in the art to identify substitutions that fall within the scope of the claims.

Applicants submit that any experimentation required to make and use additional functional homologues having substitutions falling within the scope of the pending claims would be routine. In particular, Applicants assert that at least by the earliest priority date available to the instant Application (the July 3, 2003, filing date of PA 200301044), techniques were known for producing functional homologues of binding polypeptides that would specifically bind to the same antigen as a "parent" binding polypeptide, such as those specifically identified in the specification, without any prior knowledge of the amino acid residues in the parent binding

[1] (M.P.E.P. § 2164 citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom. Massachusetts Institute of Technology v. A. B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed Cir 1983).

polypeptide that interact with the antigen to provide specificity and/or affinity. Soderlind et al., (Comb Chem High Throughput Screen 4 (2001):409-416; Exhibit 1) teach examples of these various methods (page 413, column 1, line 56 to column 2, line 1). Soderlind et al. teach that these methods include, inter alia, chain shuffling (page 413, column 2, lines 1-4) and systematic mutagenesis of the coding sequences (page 413, column 2, lines 57-59), e.g., PCR-based random mutagenesis (page 413, column 2, lines 13-15).

Moreover, Applicants provide evidence at Exhibits 2-7 that demonstrates that those of skill in the art, prior to the effective filing date of the application, did indeed make and use functional homologues of binding polypeptides, such as antibodies or antibody fragments, specific for the same antigen as the parent binding polypeptide using the methods described in the specification and/or taught by Soderlind et al. For example, Klimka et al., (Br J Cancer 83 (2000):252-260; Exhibit 2) teach production of derivative human anti-CD30 scFv antibody (hAK30) from a parent murine anti-CD30 scFv antibody (Ki-4) in which the derivative and parent antibodies share only one CDR. Klimka et al. teach, "[t]his strategy allowed the construction of a fully human anti-CD30 scFv (hAK30) with the same binding specificity as moab Ki-4, and in which only the VH(CDR3) and framework 4 sequences are derived from the parental antibody." (See, Page 253, column 1, lines 27-31). Klimka et al. produced derivative antibody hAK30 by shuffling human variable gene repertoires into the murine variable heavy and light chain genes. (See abstract at lines 10-12 and figure 1). This method of gene shuffling does not consider which amino acid residues in the parent antibody interact with the antigen to provide specificity and/or affinity when preparing derivative antibodies.

In a separate example, Marks et al., (Biotechnology 10 (1992):779-783; Exhibit 3) teach production of a derivative antibody specific for hapten 2-phenyloxazol-5-one (phOx) with up to 30-fold increased affinity relative to a parent antibody specific for phOx. (See lines 13-21 of the abstract). Marks et al. teach production of the derivative antibody by a CDR technique and that the parent and the derivative antibody share only one CDR. (See lines 13-26 of the abstract). The CDR shuffling technique randomly alters the CDRs of the parent antibody; it does not take into consideration the amino acid residues of the parent antibody's CDRs that participate in antigen binding specificity and affinity.

In another example, Rader et al., (PNAS USA, 95 (1998):8910-8915; Exhibit 4) teach production of derivative humanized antibodies specific for $\alpha v\beta_3$ having the same or higher affinity for $\alpha v\beta_3$ relative to a parent mouse antibody. (See lines 16-18 of the abstract). Rader et al. teach that four of the six CDRs of the derivative humanized antibodies differed in amino acid sequence relative to the mouse parent antibody. (See page 8912, sentence bridging columns 1 and 2. Rader et al. teach production of the derivative antibody having the same or higher affinity for $\alpha v\beta_3$ by replacing the parent mouse antibody sequences with human sequences selected from phage-displayed antibody libraries. (See lines 6-8 of the abstract). The phage-displayed approach does not consider amino acid residues present in a parent antibody's CDRs that participate in antigen binding specificity and affinity when producing a derivative antibody.

In a further example, Yang et al., (J Mol Biol, 254 (1995):392-403; Exhibit 5) teach production of derivative antibodies specific for HIV-1 gp120 having the same or higher affinity for HIV-1 gp120 than a parental antibody, b4/12. (See lines 9-12 of the abstract). Yang et al. teach that the derivative affinity matured antibody, h1.1h3.33/L1.4L3.14, having the greatest affinity for HIV-1 gp120 harbored four CDRs with amino acid sequences differing from those of the parent antibody. (See page 397, Table 5). Yang et al. teach producing the derivative antibody by a CDR walking strategy; a strategy which does not consider amino acid residues of a parent antibody's CDRs that participate in antigen binding specificity and affinity. In fact, Yang et al. teach, "[n]o specific structural information on the antibody b4/12 [parental antibody] or its antigen gp120 was available to guide the design of Fab libraries." (See Page 393, column 1, lines 32-34).

In another example, Barbas et al., (PNAS USA, 91 (1994):3809-3813; Exhibit 6) teach successful affinity maturation of a parent neutralizing human antibody specific for HIV-1 gp120 polypeptide by randomly introducting amino acid residue substitutions in two CDRs, heavy chain CDRs 1 and 3, of the parent antibody. (Page 3810, column 1, line 63 to column 2, line 8). Barbas et al. teach that despite the random introduction of amino acid substitutions into the parent antibody, derivative antibodies with improved affinity were produced. Barbas et al. teach, "[t]he present study shows the feasibility of improving antibody affinity and function where specific structural information on both antibody and antigen is not available and the antibody already possesses high affinity." (See page 3812 at lines 6-9).

In another example, Wu et al., (PNAS USA, 95 (1998):6037-6042; Exhibit 7) teach production of derivative antibodies $\alpha v\beta_3$ having 90-fold greater affinity than a parent antibody. (See lines 6-8 and lines 17-22 of the abstract and page 6042, column 1, lines 1-2). The derivative antibody having 90-fold greater affinity than the parent antibody comprised two CDRs with amino acid sequences differing from those in the parent antibody, the heavy chain CDR3 and the light chain CDR3. (See Table 3 on page 6041). Wu et al. also teach making the derivative antibody without prior knowledge of information regarding the interaction of the parent antibody with $\alpha v\beta_3$. Specifically, Wu et al. teaches, "[i]n the complete absence of structural information about the Vitaxin-$\alpha v\beta_3$ interaction, phage-expressed antibody libraries for all six Ig heavy and light chain complementarity-determining regions were expressed and screened by a quantitative assay to identify variants with improved binding to $\alpha v\beta_3$." (See lines 8-13 of the abstract).

As evidenced by the instant specification and exhibits 1-7, skilled artisans were readily able to make and use functional homologues of binding polypeptides that specifically bind to the same antigen as the parent binding polypeptide. Thus, the instant application in combination with the state of the art at the time the application was filed teaches persons of ordinary skill in the art how to make and use the claimed invention without undue experimentation. In light of the foregoing, Applicants request reconsideration and withdrawal of the instant rejection.

Rejections under 35 U.S.C. §112, first paragraph, written description

The Examiner has rejected claims 10-15, 18, and 19 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner contends that the instant specification does not disclose homologues of SEQ ID NO 6 having at least 60% identity to SEQ ID NO 6. As pointed out by the Examiner, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species.[2] Applicants respectfully submit that

[2] See Fed. Reg., Vol. 66, No. 4, pages 1099-1111 (2001).

the specification discloses a representative number of species to describe the claimed genus. Specifically, Applicants respectfully direct the Examiner's attention to Example 14 of the Synopsis of Application of Written Description Guidelines issued by the U.S. Patent Office, which clearly states that protein variants can meet the requirements of 35 U.S.C. §112, first paragraph, even if the specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins are routine in the art, (2) if the specification provides an assay for detecting the functional activity of the protein, and (3) the variant has some sequence relationship to the original sequence. In the instant situation, applications have provided ample evidence that procedures for making such variant proteins are routine in the art (see the discussion of Exhibits 1-7, above), the specification has provided an assay for detecting the functional activity of the protein (see Examples 2-4 of the instant specification which describe various PsaA binding assays), and finally, the variant must have some sequence relationship to the original sequence (at least 60% identity as outlined in the claims).

Given the teachings of the specification, and the correct standard as outlined above, Applicants respectfully submit that the claimed genus is fully supported by the specification so as to convey to one skilled in the art that Applicants were, in fact, in possession of the claimed invention at the time the application was filed. Based on all of the foregoing, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Rejections under 35 U.S.C. §102(b)

The Examiner has rejected Claims 1-5, 10-15, and 17-23 under 35 U.S.C. §102(b) as allegedly anticipated by Korman et al. (WO 200114424) in light of Hoogenboom (TIBs, 1997, vol 15, 62-70). In particular, the Examiner argues that Korman et al. teach an antibody having a sequence 100% identical to SEQ ID NO 6 and thus the claims are inherently anticipated by that disclosure, regardless of whether Korman et al. teach the ability of that sequence to bind PsaA.

Applicants respectfully traverse the foregoing rejection and assert that the instant claims are not anticipated by the cited art. A proper rejection of the claims requires the Examiner to show that each and every element as set forth in the claim is found, either expressly or inherently, in the asserted reference. (See, Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); "A claim is anticipated only if each and

every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."). This has not been done.

The cited art does not expressly or inherently disclose every element of the claims as they are currently amended. As a preliminary matter, we note that the cited art does not disclose SEQ ID NO:4 or any functional homolog thereof. Accordingly, the cited art does not disclose a binding polypeptide having two binding domains where the first comprises SEQ ID NO 6 or a functional homologue thereof and said second binding domain comprises the amino acid sequence of SEQ ID NO 4 or a functional homologue thereof. Since each and every element of the rejected claims is not found in the cited art, as required under 35 U.S.C. § 102(b), reconsideration and withdrawal of the instant rejection is requested.

The Examiner has also rejected Claims 1-7, 10, 17, 22, 24, 29, and 30 under 35 U.S.C. §102(b) as allegedly anticipated by one of Crook et al., (Clin Diagn Lab, 1998), Srivastava et al., (Hybridoma, 2000), or Gor et al., (Infect. Immun 2002, vol 70, 5589-95), in light of Hoogenboom. In particular the Examiner argues that the rejected claims are sufficiently broad that the generic PsaA binding disclosures of Crook et al., Srivastava, and/or Gor et al., could be combined with Hoogenboom to anticipate the instant claims.

As pointed out above, a proper rejection of the claims requires the Examiner to show that each and every element as set forth in the claim is found, either expressly or inherently, in the asserted reference. This has not been done.

The cited are does not expressly or inherently disclose every element of the claims as they are currently amended. In particular, as noted above, the cited art does not disclose SEQ ID NO:4 or any functional homolog thereof. Therefore, the cited art does not disclose a binding polypeptide having two binding domains where the first comprises SEQ ID NO 6 or a functional homologue thereof and said second binding domain comprises the amino acid sequence of SEQ ID NO 4 or a functional homologue thereof. Since each and every element of the rejected claims is not found in the cited art, as required under 35 U.S.C. § 102(b), reconsideration and withdrawal of the instant rejection is requested.

Rejections under 35 U.S.C. §103(a)

Claims 6-9, 20-21, and 23 stand rejected under 35 U.S.C. §103(a) as unpatentable over Srivastava et al. or Korman et al. in view of Kriangkum et al., (Biomolecular Engineering, 2001, vol 18, 31-34) further in view of Hoogenboom. Applicants respectfully point out that the examiner has not met his burden of establishing a prima facie case of obviousness. The Examiner must establish that one of skill in the art would have a reasonable expectation of success in obtaining the binding polypeptides encompassed by the pending claims and, in particular, as currently drafted. This has not been done.

As currently drafted the instant claims are directed to binding polypeptides comprising at least a first and a second binding domain capable of specifically binding Streptococcus pneumoniae surface adhesin A (PsaA) protein, said first binding domain comprises the amino acid sequence of SEQ ID NO 6 or a functional homologue thereof and said second binding domain comprises the amino acid sequence of SEQ ID NO 4 or a functional homologue thereof. The Examiner has not established how one of skill in the art would obtain binding polypeptides having such specific sequences based on the cited art. At best, these references may suggest that making some specified modification should be tried, however, "obvious to try" is not the applicable standard here. While KSR v. Teleflex (550 U.S. __, slip opinion at 17 (2007)) suggests that "obvious to try" may be an acceptable basis for finding obviousness in some circumstances, it does not apply in situations such as this one where the outcome, including the identification of particular sequences, could not have been reasonably predicted. (In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)).

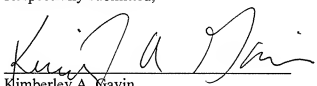
In light of the foregoing, Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness and therefore withdrawal of the instant rejection is respectfully requested.

Conclusion

To expedite allowance of this application, the Examiner is invited to telephone the undersigned if the Examiner believes a telephone call would be helpful in advancing prosecution.

Applicants believe that no fee, is due in connection with the filing of this Response. If any additional fee is due, or overpayment made, with regard to this Response, the Transmittal and Fee Transmittal (submitted in duplicate herewith) authorizes the Director to charge any such fee, and credit any overpayment, to Deposit Account No. 02-4377.

Respectfully submitted,



Dated: October 26, 2007

Kimberley A. Gavin
Reg. No. 51,723
Agent for Applicants

BAKER BOTTS L.L.P.
Customer No. 63367
30 Rockefeller Plaza
New York, NY 10112-4498
(212) 408-2500